AD_____

Award Number: DAMD17-99-1-9084

TITLE: Avoiding Late Cardiac Effects of Radiation Treatment of Breast Cancer by Simple Respiratory Maneuvers

PRINCIPAL INVESTIGATOR: Hsiao-Ming Lu, Ph.D.

CONTRACTING ORGANIZATION: Dana-Farber Cancer Institute
Boston, Massachusetts 02115

REPORT DATE: October 2001

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 074-0188

1. AGENCY USE ONLY (Leave blank)	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED
	October 2001	Annual (1 Oct 00 - 30 Sep 01)

4. TITLE AND SUBTITLE
Avoiding Late Cardiac Effects of Radiation Treatment of Breast Cancer by Simple Respiratory Maneuvers

5. FUNDING NUMBERS
DAMD17-99-1-9084

6. AUTHOR(S)
Hsiao-Ming Lu, Ph.D.

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
Dana-Farber Cancer Institute
Boston, Massachusetts 02115

E-Mail: **hmlu@lroc.harvard.edu**

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSORING / MONITORING AGENCY REPORT NUMBER

11. SUPPLEMENTARY NOTES
Report contains color

12a. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

12b. DISTRIBUTION CODE

13. ABSTRACT ***(Maximum 200 Words)*** The second year, also the final year, of this contract is for completing the software development of the patient position control system and then performing phantom testing and patient testing at both CT-simulator where the patient's treatment is planned and at the treatment unit where the treatment is delivered. The software development has achieved all the goals: an efficient marker recognition algorithm has been developed and the user interface for the position control module has been enhanced by providing real-time plot of marker positions and by implementing automated point capture procedures. Moreover, a database and the associated browser have been created to handle the patient data in a network environment to make data available both at the simulator and at the treatment unit. Phantom test of the overall accuracy of the system has been conducted at CT-simulator with satisfactory results. Significant efforts have also been made to experiment in making smaller hollow hemispherical markers that can be more accurately placed on patient's skin surface and yet do not interfering with the radiation treatment. The planned tests using both phantom and real radiation patients were not conducted due to the unexpected delay in installing the system in the treatment room. For this reason, a no-cost extension was filed and approved.

14. SUBJECT TERMS	15. NUMBER OF PAGES
Radiation therapy, breast cancer treatment, patient position control	15
	16. PRICE CODE

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT
Unclassified	Unclassified	Unclassified	Unlimited

Table of Contents

IV. INTRODUCTION

1. CLICNICAL PROBLEM, BACKGROUND AND HYPOSHTESIS

Grant DAMD17-99-1-9084 supports the development of a new radiation therapy treatment technique for left-sided breast cancer patients. The new technique uses simple respiratory maneuvers to reduce radiation to cardiac tissues to avoid possible late cardiac effects. Specifically the grant supports the development and testing of a patient position monitoring system, which will ensure that the radiation treatment is delivered accurately and only when the patient is at the optimal body configuration during the respiratory maneuvers. The grant also supports the development of a treatment planning software that will promptly evaluate quantitatively the benefit of the new treatment technique for a specific patient.

Radiation therapy (RT) plays an important role in patients with early-stage breast cancer both for a) improved quality of life through its use with lumpectomy in providing breast-conserving local therapy and b) possibly improved survival when used as comprehensive local-regional treatment in conjunction with systemic therapy[1].

An important caveat in considering the effects of local radiation therapy is its toxicity; early reports demonstrated that post-mastectomy RT was associated with an increased cardiac mortality from outdated RT techniques[2-10]. With modern RT techniques, e.g., CT-simulation, cardiac volumes can be delineated more accurately geometrically relative to the radiation field and treatment plans can be more optimized to reduce the radiation to the heart. However, in many cases, the radiation beam still has to traverse a non-negligible portion of the heart in order to treat all of the breast tissue and the concave chestwall to eradicate the residual disease. There is great concern worldwide about the possible late cardiac effects of RT when used in conjunction with cardiotoxic adjuvant chemotherapy. As the incidence of breast cancer increases and the age of the patient population decreases, the issue of late cardiac toxicity will become more important and it is imperative that we search for safer techniques to deliver the radiation treatment.

In the current technique of RT, the patient breathes normally while receiving the radiation treatment. In a recent study of a group of patients, we found that holding breath after a deep inspiration can significantly reduce the cardiac volume in the tangent treatment fields. For many patients, deep inspiration can push cardiac tissues completely out of the treatment fields.

The clinical rational and hypothesis for this work is that we can develop a treatment technique that delivers the radiation only when the patients hold their breath after a deep inspiration. In a typical first-course breast cancer RT treatment, the radiation dose is given by 22-30 fractions over the period of 4.5 - 6 weeks. On each day, the treatment uses two tangent fields, the medial tangent field and the lateral tangent field, to deliver the radiation. For each beam, the actual time receiving the radiation is about 20-30 seconds, depending on the prescribed dose and/or the patient's anatomy. From our experience with the breath-holding study mentioned above, we found that patients can hold their breath for 20 seconds without any difficulty. If we use 10 seconds of the 15-20 seconds breath-holding duration to deliver the radiation, it only requires 2-3 breath-holding cycles to deliver the total radiation required for each beam. Fig. 1 illustrates the treatment time sequence for one breath-holding cycle.

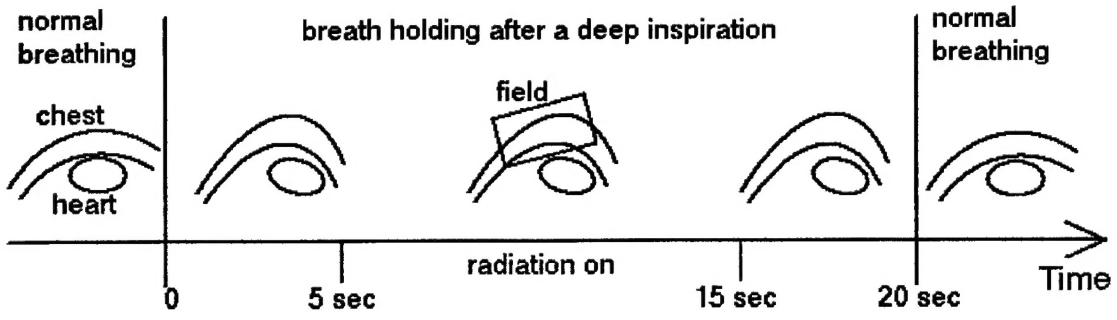

Fig. 1. Treatment time sequence for one breath-holding cycle.

2. SPECIFIC RESEARCH OBJECTIVES

2.1 Patient position monitoring system

In order for the patient to receive the radiation treatment to the exact anatomical location as planned, it is important that the patient's body position is the same from the treatment planning facility, i.e., the CT-simulator, to the treatment linear accelerator, from one breath-holding cycle to the next, from one treatment beam configuration to another beam, and from one day to another day throughout the whole treatment course of 22-30 days. This requires a monitoring system that can instantaneously track the patient's breath-holding state. Such a system can be developed using a computer interfacing with a three-dimensional (3D) digitization device, for example, the POLARIS system that uses infrared light to track instantaneously the position of infrared reflective markers in space. By placing these markers on the patient's chest and tracking the three-dimensional coordinates of the spheres, one can monitor the motion of any point on the patient's chest with sub-millimeter accuracy.

The development of this patient position/posture monitoring system involves 1) the development of a software interface between the POLARIS system and the host computer, 2) the development of tools for capturing patient body configuration information, 3) the testing of the accuracy and active volume of the POLARIS system and the reflective markers in CT simulator and linear accelerator treatment facilities, 4) the development of software for the calibration of the tracking system to the coordinate system of the facilities (CT-simulation/treatment linear accelerator), 5) the development of the a software for tracking markers placed on patients and evaluating if the patient entered the breath holding configuration for treatment, 6) the testing of tracking system by phantoms, and finally 7) the testing of the system on real patients.

2.2 Special functions in treatment planning software

The breath-holding treatment method requires special treatment planning functions that are not available in current commercial CT-simulation/treatment planning software systems. These include 1) the accurate and rapid calculation of the cardiac volume in the field at the CT simulation for both the normal-breathing and breath-holding configuration to determine if the breath-holding treatment technique is necessary for a specific patient, 2) automated or semi-automated field placement procedure for tangential fields with full field matching to allow the planner to rapidly evaluate different treatment geometries, 3) accurate dosimetric corrections for the extremely low lung density due to deep inspiration, 4) convenient interface with the patient position/posture monitoring system.

V. BODY OF ANNUAL REPORT

OVERALL PROGRESS

For the second year, also the final year, of the project, we focused on the continued development of the patient position monitoring system. This includes 1) completing the software development, 2) testing the system on phantoms, and 3) testing on real radiation therapy patient without interfering with the actual treatment. While tasks 1 and 2 have been essentially completed, task 3 was delayed. This delay is mainly due to the unexpected difficulty met in installing the POLARIS camera system in the linear accelerator room where task 3 will be conducted. (Please see attached memo for details.) Accordingly, a no-cost extension has been applied and approved.

Significant efforts have also been made in improving the infrared reflective markers to be used in tracking changes of patient's body configuration. In the previous year, we have evaluated the accuracy of a hemispherical marker produced experimentally by Northern Digital Inc. As discussed in the previous annual report, these hemispherical markers can be more accurate in tracking the position of a point on the patient's skin surface than the whole-sphere markers originally considered, because the center of the hemisphere can be placed exactly at the point to be tracked. However, these markers have a diameter of 12 mm and are not transparent. It is actually quite difficult to place the markers on a soft skin surface such that the center of the marker is exactly at the point to be monitored. It was found that variations between placements could be as large as 3 mm. This is clearly not acceptable if we want to accurately monitor the patient's body configuration through the coordinates of these markers. A reflective marker with a smaller diameter, e.g., 6 mm, is needed.

SPECIFIC PROGRESS

Software Development

A) An efficient and reliable marker recognition algorithm. The system monitors the patient position by tracking the multiple reflective markers placed on the patient's chest and then comparing these marker positions with their intended positions determined at the time of simulation or in a prior session. However, the POLARIS camera system reports the coordinates of the markers in an arbitrary order. Thus, a recognition algorithm has to be used to identify these coordinates with the individual markers on the patient. The algorithm has to accommodate not only when the patient is approximately in the treatment position, but also the situation when the patient has been set to the correct body posture but still different from their treatment position by a translation and/or a rotation of the treatment table. This is important because it will enable the system to help with setting up the patient in the correct body posture, a critical step for an accurate radiation therapy treatment.

B) User interface enhancement. The software user interface in the patient position control mode is further developed. Specifically, we added 1) functions to allow the user to modify interactively the threshold values for makers, 2) real time marker position variation display, and 3) automated procedures for capturing, updating, and saving marker patterns. (See Fig. 2) These components are essential in making the system efficient enough to be used in a clinical setting.

C) Database for patient position data. The patient's position monitoring system will generate a large amount of data. For each simulation or treatment session, a patient will undergo several breath holding cycles, and for each cycle, the system will track and store the positions of reflective markers on the patient at a minimum rep rate of 10hz for a period of 20 seconds. Moreover, these data will be generated both at CT-simulator and treatment units. Therefore, it is necessary to have an efficient

system to manage the data for multiple patients with multiple treatment sessions and at multiple locations across the network. We created a database using Microsoft Access to store the patient information and all geometric data regarding patient's radiation treatment, i.e., treatment course, fields, body control marker positions, etc. We have developed a browser application to review patient data structures and database interfaces for all the applications relevant to patient body position control. Fig. 3 shows the browser application user interface. The database resides on a Windows NT server and can be accesses by all the applications from all simulation and treatment units through ODBC (Open DataBase Connectivity) database drivers.

Hemispherical reflective markers with smaller diameters

D) The search for smaller hemispherical markers. We first contacted Northern Digital Inc., who produced the large hemispherical markers. Unfortunately, the company does not want to investigate any further. To our knowledge, Bioengineering Technology System (BTS) is the only company that produced hemispherical markers with smaller diameters, e.g., < 5 mm. We have obtained a few of such markers and found that they are workable as far as tracking is concerned. However, unlike the hemispherical markers made by Northern Digital Inc that is hollow, the base of these hemispherical markers are solid and are made of rubber-like material. This could potentially increase the radiation dose to the patient skin surface at the points where the markers are placed, if the markers happen to be in the treatment field, a situation that cannot always be avoided. Moreover, the quality of the reflective coatings on these markers is not consistent and they do not always cover the side area well. When the markers are at an angle from the infrared camera, as is always the case when the markers are placed on the patient's chest, tracking can be severely affected. It was concluded that these markers were inappropriate for the project.

E) Making the reflective markers ourselves. By using plastic sheets and thermal expansion, we were able to make hemispherical shell shapes with a diameter of only 6 mm. We then applied adhesive tapes with reflective coating on the hemispherical plastic shape. It is found that these smaller markers are more accurate in placement and since it is hollow, it will not significantly increase the radiation dose to the patient skin surface. However, the process of making these markers is all manual and very time consuming. Since the markers cannot be autoclaved without damages to the coating, they can be used only once. For a reasonable control of the patient's posture and position during treatment, we have to use at least seven. Thus, a regular treatment course of 25 fractions for one patient will require a minimum of 25 x 7 = 175 markers. For our study involving 5-6 patients as specified in the protocol, we would need about 1000 markers. This is a significant amount of manual labor. We are in the process of looking for a more efficient method of making the markers, or a different cleaning procedure so that the markers can be used more than once.

Phantom Tests

F) System accuracy test at CT-simulator. A breast phantom was used to conduct the test. Eight markers were placed on the phantom as shown in Fig. 4(a) to track seven points on the phantom (The two close markers are used to track a single point, which is required by the marker recognition method used in the system.) The hemispherical markers have a radio-opaque bee-bee at the center of its base. These bee-bees are visible in the CT images and their positions can be obtained accurately. (The transverse coordinates, i.e., left-right and anterior-posterior, are obtained from axial CT images, while the longitudinal positions, i.e., superior-inferior, are obtained from scout images to avoid errors introduced by the finite spacing between axial images.) Since the markers are hemispherical and the bee-bees are at the center of the hemisphere, the maker positions captured by the patient position

control system should agree with the positions of the bee-bees obtained from the CT-scan. Table 1 shows the differences between the two. The maximum difference is 1.5 mm, while the average over all the points is less then 0.6 mm. These values are well within the expected accuracy of the system. These results demonstrate that the overall accuracy of the system, including calibration, coordinate transformation, marker preparation, etc., is satisfactory.

G) Motion tracking. To evaluate the ability of the system to monitor changes in patient's posture or position, we used a phantom that can generate a periodic motion. The periodicity is set to 6 seconds with an amplitude ±1 cm. This motion simulates closely the patient's motion due to regular breathing. A couple of markers are placed on the phantom and their position changes were monitored by the system. Fig. 5 shows the software interface at the time of the testing. The graph at the bottom of the screen shows the periodic change in one coordinate. At the rep rate set at 10Hz, the system can accurately track the change in marker positions. Naturally, the higher the rep rate, the more sensitive the system can be. However, the limit for the rep rate is determined by the number of markers the system has to track at the same time, and ultimately determined by the CPU speed of the computer.

Fig.2. User interface for patient position control program module. The crosses represent the current positions of the points on the patient's body surface reported by the camera, while the small yellow dots are the correct positions for these points. The bottom graph displays the coordinate of the selected point as a function of time. The graph shows almost no change in coordinate, because the phantom under study is rigid. For real patients, a larger fluctuation will be expected.

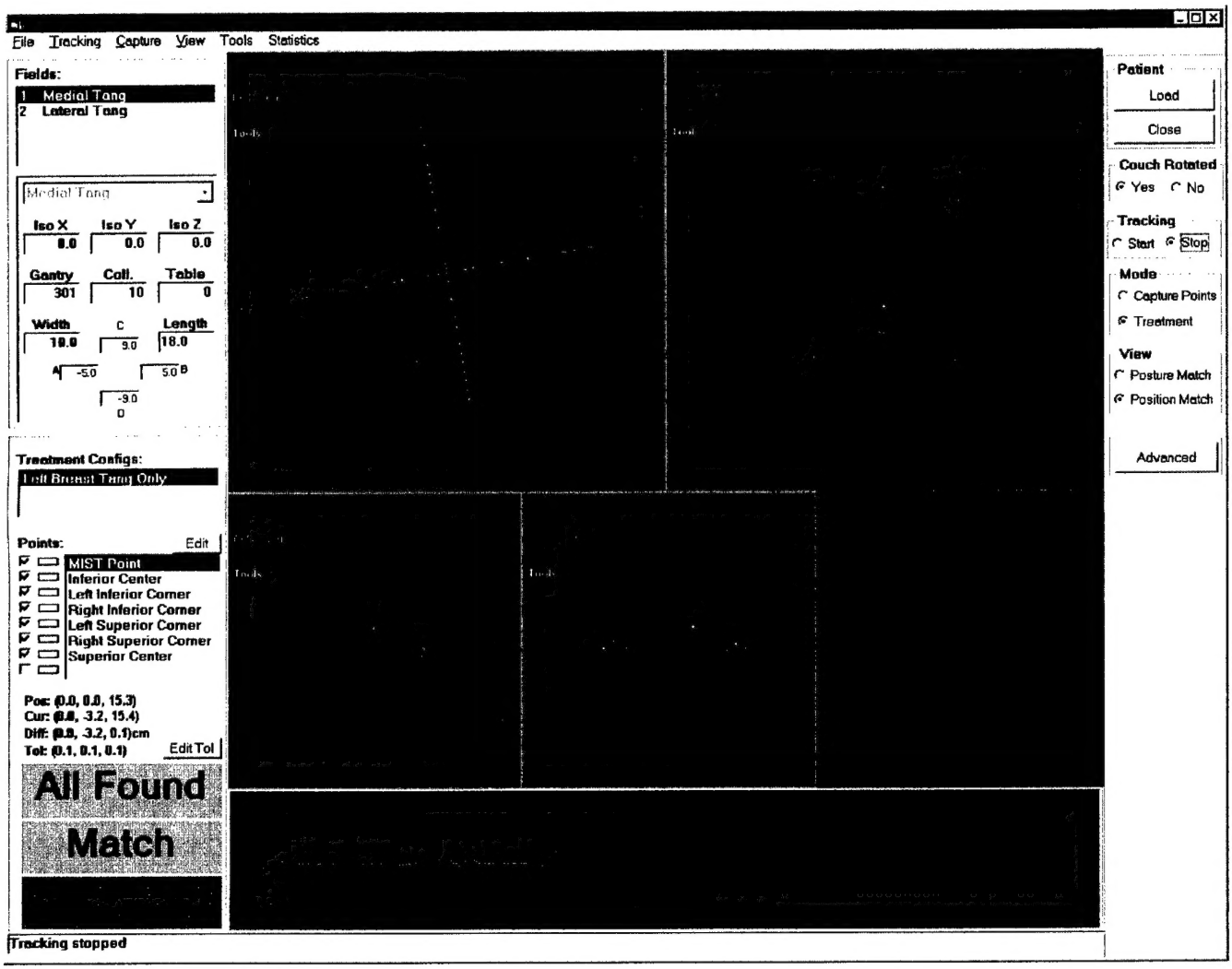

Fig. 3. User interface for database browser application.

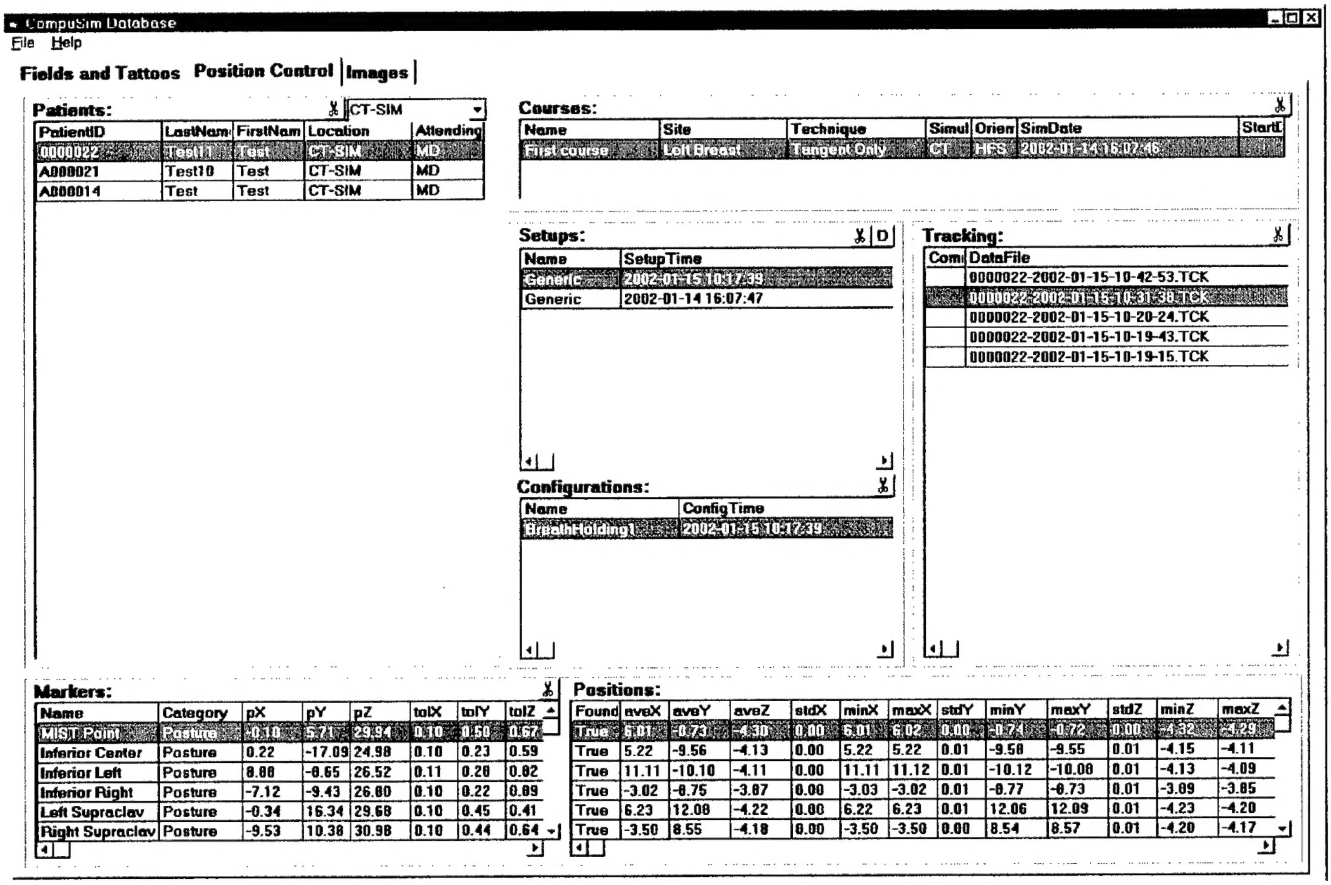

Fig. 4. 3D surface reconstruction of the breast phantom used in testing the accuracy of the patient position system at CT-simulator. Eight markers are placed on the phantom for tracking the seven points.

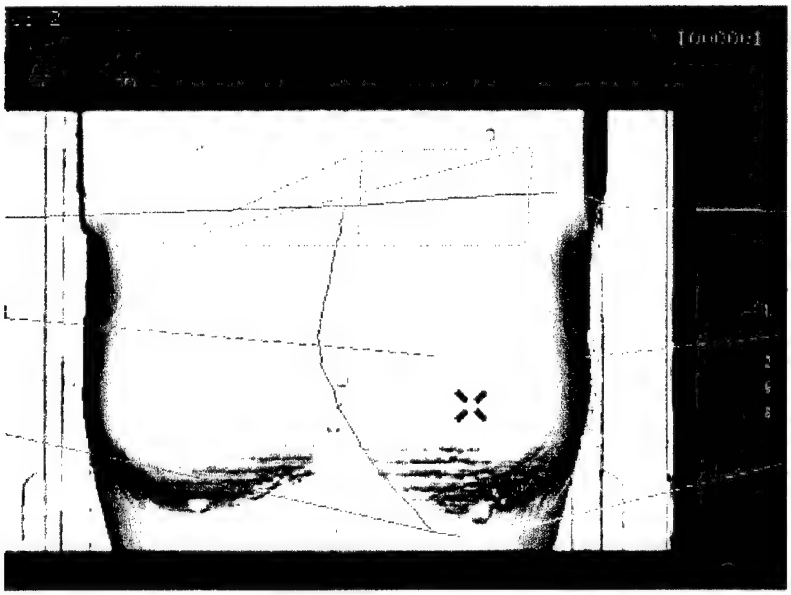

Fig. 5. User interface for the motion tracking test.

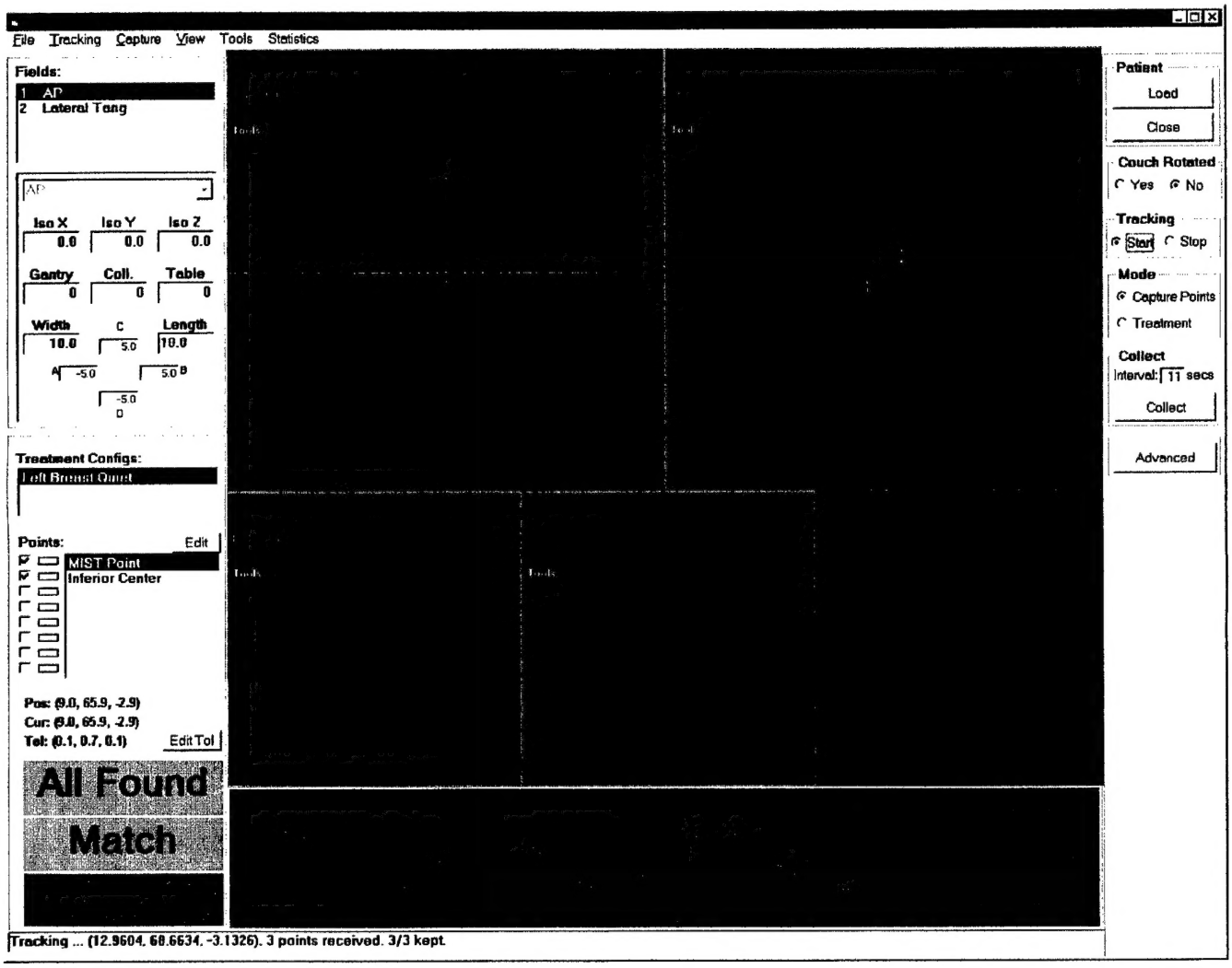

Table 1. Differences in coordinates (mm) between captured marker positions and those obtained from CT. RAS is the internal coordinate system of the CT images. The R and A coordinates were obtained from the axial images. However, the S coordinates were obtained from a frontal scout view to avoid errors introduced by the finite spacing between adjacent axial images.

For Test01, Test T000001

	Mist	Inf. Cent	LT Cent	RT Cent.	LT Sup	RT Sup	Sup Cent	average	max	min
R=	0.30	0.40	0.30	0.10	1.00	0.60	0.10	0.40	1.00	0.10
A=	0.50	1.30	0.00	0.10	1.30	0.80	0.10	0.59	1.30	0.00
S=	0.70	0.20	0.40	0.20	0.70	**1.50**	0.30	0.57	**1.50**	0.20

VI. KEY RESEARCH ACCOMPLISHMENTS

The software development is completed for the patient position monitoring system using infrared camera system (POLARIS) and reflective markers placed on patient body surface.

Phantom testing on the overall accuracy of the system at Ct-simulator is completed.

VII. REPORTABLE OUTCOMES

None.

VIII. CONCLUSIONS

The main goal for the second year, also the final year, of the project is to complete the development of the patient position monitoring system and then perform the phantom testing and patient testing both at the CT-simulator where the patient's treatment are planned and at the treatment unit where the treatment is delivered. While the system development has achieved all the goals, the testing on phantom was only conducted at CT-simulator. The delay of phantom testing and patient testing at the treatment unit is due to the unexpected difficulties in installing the system in the treatment unit. As explained in the filed application for extension (attached), the configuration of the treatment machine made it very difficult to mount the infrared camera system in an appropriate location with full functionality of monitoring the markers positions on the patients and without interfering the routine use of the treatment machine hardware. Efforts are underway to solve this problem.

IX. REFERENCES

1. Harris JH, Lippman, ME, Veroniesi U, Willett W. Breast cancer. New England Journal of Medicine 1992; 327:473-480.

2. Corn BW, Trock BJ, Goodman RL. Irradiation-related ischemic heart disease. J Clin Oncol 1990; 8:741-50.

3. Cuzick J, Stewart H, Rutqvist L, et al. Cause-specific mortality in long-term survivors of breast cancer who participated in trials of radiotherapy. J Clin Oncol 1994; 12:447-53.

4. Fuller SA, Haybittle JL, Smith RE, Dobbs HJ. Cardiac doses in post-operative breast irradiation. Radiother Oncol 1992; 25:19-24.

5. Gyenes G, Fornander T, Carlens P, Rutqvist LE. Morbidity of ischemic heart disease in early breast cancer 15-20 years after adjuvant radiotherapy. Int J Radiat Oncol Biol Phys 1994; 28:1235-41.

6. Haybittle JL, Brinkley D, Houghton J, A'Hern RP, Baum M. Postoperative radiotherapy and late mortality: evidence from the Cancer Research Campaign trial for early breast cancer. Bmj 1989; 298:1611-4.

7. Host H, Brennhovd IO, Loeb M, Hst H. Postoperative radiotherapy in breast cancer--long-term results from the Oslo study. Int J Radiat Oncol Biol Phys 1986; 12:727-32.

8. Jones JM, Ribeiro GG. Mortality patterns over 34 years of breast cancer patients in a clinical trial of post-operative radiotherapy. Clin Radiol 1989; 40:204-8.

9. Lipshultz SE, Colan SD, Gelbar RD, Perez-Atayde AR, Sallan SE, Sanders SP. Late cardiac effects of doxorubicin therapy for acute lymphoblastic leukemia in childhood. N Engl J Med 1991; 324:808-815.

10. Rutqvist LE, Lax I, Fornander T, Johansson H. Cardiovascular mortality in a randomized trial of adjuvant radiation therapy versus surgery alone in primary breast cancer. Int J Radiat Oncol Biol Phys 1992; 22:887-96.

11. Lu HM, Cash E, Chen MH, Chin L, Manning W, Harris J, Bornstein B. Reduction of cardiac volume in left-breast treatment fields by respiratory maneuvers: a CT study. Int J Radiat Oncol Biol Phys 2000; 47(4): 895-904.